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ARTICLE

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Replacement therapy in pregnant women with von Willebrand disease during delivery: Factor levels and pharmacokinetics

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Abstract

Limited data are available on VWF activity (VWF:Act) and factor VIII (FVIII:C) levels during delivery after VWF/FVIII concentrate administration in women with von Willebrand disease (VWD). We aimed to evaluate treatment with a specific VWF/FVIII concentrate on factor levels in women with VWD during delivery and the postpartum period. A retrospective single-center study was conducted between January 1, 2008, and August 1, 2022. Pregnant women treated with Haemate®P during delivery were included if they had ≥2 consecutive VWF:Act and FVIII:C measurements post-infusion. VWF:Act/FVIII:C levels were compared to predefined target levels. A population pharmacokinetic (PopPK) model was developed, estimating VWF and FVIII pharmacokinetics after Haemate®P administration. Nineteen women were included. Targeted VWF:Act/FVIII:C peak levels were achieved after the first infusion (≥1.00 IU/mL, $n = 12$; ≥1.50 IU/mL, $n = 5$), and all VWF:Act/FVIII:C trough levels remained ≥0.50 IU/mL during first 72 h of treatment. All women had pretreatment FVIII:C levels ≥1.00 IU/mL, except one woman with type 2N, which was significantly higher than FVIII:C levels during the third trimester (median increase: 0.42 IU/mL, interquartile range: [0.12–0.92]). FVIII:C trough levels increased during treatment, median 2.05 IU/mL [1.65–2.71]. Nine women (47%) experienced postpartum hemorrhage and no thrombosis occurred. A one-compartment PopPK model adequately described VWF:Act/FVIII:C levels. Targeted VWF:Act/FVIII:C peak levels were achieved with the prescribed dosing regimens. VWF clearance was similar to that in nonpregnant individuals. Both pretreatment and FVIIIC trough levels during treatment were high with reduced FVIII clearance. Monitoring VWF:Act/FVIII:C levels is recommended for optimizing target levels and enriching the current PopPK model, improving VWF:Act/FVIII:C level predictions, and achieving more effective dosing.

INTRODUCTION

Women with von Willebrand disease (VWD) have an increased risk of bleeding during pregnancy and delivery. Postpartum hemorrhage (PPH) is categorized into primary PPH, which occurs within 24 h after delivery, and secondary PPH, occurring from 24 h up to 6 weeks postpartum.[1] Based on retrospective studies, the incidence of PPH in women with VWD varies between 5.5% and 44%.[2–5] Moreover, James et al. report an odds ratio of 1.5 (confidence interval [CI]: 1.1, 2.0) for the development of PPH with a higher likelihood of being transfused (OR, 4.7; 95% CI: 3.2, 7.0) in a large study in women with and without VWD.[6]

In healthy women, the hemostatic balance shifts toward a procoagulant state during pregnancy to prevent excessive bleeding during delivery and in the postpartum period. This is partly due to an increase in VWF and FVIII levels.[7–9] This physiological increase of VWF and FVIII levels also occurs during pregnancy in women with VWD, especially in the third trimester. Most women with type 1 VWD present with a sufficient increase in VWF and FVIII levels to prevent bleeding. However, in other women, especially those with type 2 and

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type 3 VWD, there is either none or an insufficient increase of VWF and FVIII levels.[10,11] Therefore, due to this interindividual variation in the increase of VWF and FVIII levels, it is recommended to measure factor levels during the third trimester of pregnancy.[12] According to international guidelines, if VWF and FVIII levels are <0.50 IU/mL in the third trimester, prophylactic treatment with desmopressin or VWF-containing concentrates is prescribed to prevent PPH.[13] Desmopressin is, however, only an option for women with a previously demonstrated adequate increase in FVIII and VWF levels after testing with desmopressin. Importantly, guidelines in some countries recommend against desmopressin use due to potential neonatal complications.[14] In type 3 VWD patients and patients with type 1 and 2 who do not respond to desmopressin, VWF/FVIII concentrate is the choice of treatment.[12,13] Nevertheless, which target levels are minimally needed to achieve adequate hemostasis during delivery is still unknown. Due to a lack of evidence, the international guideline does not specify target levels.[13] However, despite prophylactic treatment with VWF/FVIII concentrates to prevent PPH in women with VWD, studies show that PPH incidence also remains high compared to the general population.[4,15] Therefore, in the Netherlands, the national guideline was updated in 2020, increasing the VWF and FVIII target levels at the time of delivery from 1.00 to >1.50 IU/mL.[12] In addition, other guidelines for PPH management from several countries recommend a target peak level of VWF and FVIII > 1.00 IU/mL at the time of delivery.[13,16,17] However, in healthy women, VWF rises to >3.00 IU/mL and FVIII reaches levels up to 2.00 IU/mL.[18] This suggests that in clinical practice significantly higher VWF and FVIII target levels may be required. Furthermore, the lack of studies that have assessed factor levels during delivery makes it difficult to determine if these prescribed factor levels are achieved and which factor levels should be maintained. This is particularly important as pregnancy may significantly affect the pharmacokinetics (PK) of coagulation factors due to physiological changes, especially a larger volume of distribution. Potentially, this may require prescribing different dosing regimens of VWF/FVIII concentrates in pregnant women compared to those applied in nonpregnant individuals.

The aim of this study is to assess VWF and FVIII levels following treatment with a specific VWF/FVIII concentrate during delivery and in the postpartum period in women with VWD. The second aim was to develop a population PK model (PopPK) for VWF/FVIII concentrate in women during delivery and postpartum period to estimate PK of VWF and FVIII.

METHODS

This single-center retrospective observational study was conducted in a large hemophilia treatment center in the Netherlands (Erasmus MC, University Medical Center Rotterdam). All included patients participated in the "Willebrand in the Netherlands" (WiN) study and/or "Willebrand in the Netherlands" prospective study (WIN-pro study) (ClinicalTrials.gov:NCT03521583). The inclusion criteria of both studies were similar and were hemorrhagic symptoms or a family history of VWD, and historically lowest VWF antigen level (VWF:Ag) and/or VWF activity (VWF:Ab) and/or VWF collagen binding activity (VWF:CB) ≤0.30 IU/mL and/or factor VIII activity (FVIII:C) ≤0.40 IU/mL.[19] Both studies were approved by the Medical Ethical Committee and have been described extensively in previous publications.[19–22]

STUDY POPULATION

Pregnant women with VWD who were treated with a specific VWF/FVIII factor concentrate (Haemate P®) during delivery and had at least two constructive VWF:Act/FVIII:C measurements during treatment were included from January 1, 2008, until August 1, 2022. Women were excluded if delivery and postpartum care occurred at another hospital and if they did not participate in the previously mentioned "WiN" and "WiN-pro" studies. Haemate P® was the most often used VWF/FVIII concentrate at our center during this period for patients with VWD. Haemate P® is a plasma-derived factor concentrate and contains VWF and FVIII with a VWF/FVIII ratio of 2.4:1.[23] VWF:Act and FVIII:C measurements during treatment were performed regularly in order to evaluate treatment.

Data collection

Patient, obstetric, and treatment characteristics were collected retrospectively from electronic patient files. Patients characteristics included age, body weight in the third trimester, type of VWD, historically lowest levels of VWF (including VWF:Activity (VWF:Act); VWF:Antigen (VWF:Ag), VWF:collagen binding activity (VWF:CB), FVIII:C, and ABO blood group). Type 1 VWD was defined as having a VWF:Act/VWF:Ag ratio >0.7, whereas type 2 VWD was categorized as VWF:Act/VWF:Ag ratio ≤0.7. FVIII:C levels were measured by a one-stage clotting assay. Different VWF activity (VWF:Act) assays were used throughout the years. Between 2005 and 2012, a monoclonal antibody assay for VWF (VWF:Ab) was used with von Willebrand Factor Activity kit on a Sysmex CA-1500 analyzer (TOA medical Electronics Co., LTD.). Subsequently, from 2012 onward, the VWF glycoprotein 1b binding (VWF:GP1bM) assay with the INNOVANCE VWF Ac' reagent on Sysmex CS5100 or CS2500 analyzer was used (TOA medical Electronics Co., LTD.).

Obstetric characteristics were delivery mode and obstetric risk factors for PPH based on the California Maternal Quality Care Collaborative (CMQCC) guideline,[24] such as prior cesarean section or uterine surgery, history of PPH, presence of polyhydramnios, placenta abnormalities, HELLP (hemolysis elevated liver-enzymes low-platelet-count) syndrome, prolonged labor/Induction (>24 h), retained placenta and uterine abnormalities during and after delivery (uterine atony, uterine rupture), and neonatal macrosomia. A retained placenta was defined as the necessity of manual placental removal and macrosomia as a neonatal weight of ≥4000 g.[25,26] In cases where there was no documentation of obstetric risks, these were registered as unknown. An exception was made for obstetric risks such as HELPP syndrome and uterine rupture, as these would always have been documented as treatment is absolutely necessary. Therefore, if these risk factors were not mentioned in the patient file, it was considered absent. We defined PPH according to the World Health Organization (WHO) definitions, as primary PPH when blood loss ≥500 mL within 24 h postpartum in case of vaginal delivery or when blood loss ≥1000 mL in case of cesarean section. Secondary PPH was defined as significant blood loss from 24 h up until 6 weeks postpartum.[27] Treatment characteristics included VWF and FVIII levels during the third trimester of pregnancy and shortly before treatment with the specific VWF/FVIII concentrate, timing and dosing of VWF/FVIII concentrate, achieved VWF and FVIII levels during and after delivery, mode of infusion (continuous or bolus infusion) of VWF/FVIII concentrate, co-medication with effects on hemostasis (desmopressin, tranexamic acid, low molecular weight heparin, nonsteroidal anti-inflammatory drugs), and treatment duration.

Study outcomes

The objective of this study was to evaluate the treatment with VWF/FVIII concentrate (Haemate®P) on factor levels in women with VWD during delivery and the postpartum period. This evaluation included:

TABLE 1 Dutch guidelines for prophylactic replacement therapy with VWF/FVIII concentrates, for example, VWF:Act and FVIII:C target levels during treatment.

	Dutch guideline 2009	Dutch guideline 2020
PPH hemostatic management with VWF/FVIII concentrate		
Cut-off level		
	VWF or FVIII <0.50 IU/mL	VWF or FVIII <0.80 IU/mL
Target level		
At delivery	Peak VWF:Act and FVIII:C ≥1.00 IU/mL	Peak VWF:Act and FVIII ≥1.50 IU/mL
Postpartum period	Not specified	*Vaginal delivery* Trough VWF:Act and FVIII ≥0.50 IU/mL during 3 days *Cesarean section* Trough level VWF:Act and FVIII ≥0.50 IU/mL during 5 days, than VWF:Act and FVIII >0.30 IU/mL

Abbreviations: FVIII, factor VIII; IU/mL, international units/milliliter; PPH, postpartum hemorrhage; VWF:Act, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen.

(1) a comparison of observed VWF:Act and FVIII:C levels to predefined targeted factor levels according to guidelines and (2) construction of a PopPK model to analyze the volume of distribution (Vd) and clearance (CL) of VWF:Act and FVIII:C during treatment. Study outcomes were based on data obtained from the first reported pregnancy of the included women. In the case of women with multiple pregnancies, extra analyses were conducted on these pregnancies to compare each pregnancy within the same woman, aiming to assess observed differences in factor levels and other factors that are potentially associated with the occurrence of PPH.

Table 1 summarizes PPH hemostatic management according to the Dutch guidelines of 2009 and 2020, including the specified cut-off levels for prophylactic treatment and target factor levels during treatment at the time of delivery. Since the study population was selected from 2008 until 2022, both guidelines were used to assess guideline adherence, depending on which one was applied. Peak levels were defined as measurements taken within 2 h after VWF/FVIII concentrate administration and trough levels were defined as measurements taken before the next administration of VWF/FVIII concentrate or at least 12 h after administration when no subsequent infusion was given.

Based on observed VWF:Act and FVIII:C during treatment, a PopPK model was developed to estimate the PK parameters, VD, and CL of VWF and FVIII. These PK parameters were compared to the established PK parameters of nonpregnant individuals by Bukkems et al. to determine whether changes in PK are important in pregnancy.[28] Data from the first documented pregnancy were used to develop the PopPK model.

Statistical analysis and population pharmacokinetic modeling

Descriptive data are presented as numbers with percentages for categorical variables and medians with an interquartile range (IQR) for continuous variables. In cases where data were not normally distributed, the nonparametric Mann–Whitney *U* test was used to compare groups, and the Wilcoxon Signed-Rank test was used for related continuous variables.

PopPK modeling was used to estimate the PK parameters, Vd and CL of VWF and FVIII. The PopPK analysis was performed using a nonlinear mixed-effects modeling approach with the software NONMEM (version 7.3; ICON Development Solutions). Development of the model was performed in three steps: (i) selection of the structural model, (ii) adding inter-individual variability (IIV) of the PK parameters and selection of the statistical error model (additive, proportional, or a combined error model), and (iii) a covariate analysis to investigate whether patients characteristics explained the IIV in the covariate model. One- and two-compartment model approaches were tested as a potential structural model. A priori, body weight was included as a covariate on both CL and V using allometric body weight scaling.

Covariates that were present in the data set included body weight in the third trimester, calculated lean body mass,[29] age, type of VWD, blood group, endogenous VWF:Act and FVIII:C levels in the third trimester, mode of delivery (vaginal delivery or cesarean section), and duration of delivery. Duration of delivery was defined as the time in hours between the active dilation phase and childbirth. Continuous covariates (lean body weight, age, duration of delivery) were implemented in the model using power functions, standardized for a typical individual of 70 kg, or the median value of the covariate. Categorical covariates, such as type of VWD and blood group, were included in the PK model to investigate whether this affected specific PK parameters.

Regarding internal validation, a prediction-corrected visual predictive check (pcVPC) was performed to evaluate the predictive performance of the final model. The pcVPC assesses graphically whether simulations from a model can reproduce the observed data. Moreover, a nonparametric bootstrap was performed. This technique involved generating 1000 bootstrap data sets by resampling from the original data set. From the bootstrap, we compared the median parameter values and the 2.5th–97.5th percentile estimates with the final model estimates. More information about model development and internal validation can be found in the Supporting Information Materials.

RESULTS

A total of 19 women met the inclusion criteria (Figure 1). Six (42%) women with type 1 VWD and 13 (58%) women with type 2 VWD. Eleven (58%) women had two or more pregnancies. For women with type 1 VWD, the median historical lowest measured VWF:Ag and VWF:Act level were 0.10 IU/mL IQR [0.06–0.24] and 0.18 IU/mL IQR [0.10–0.26], respectively. For women with type 2 VWD, the median historical lowest measured VWF:Ag and VWF:Act level were, respectively, 0.29 IU/mL IQR [0.21–0.43] and 0.11 IU/mL IQR [0.08–0.27] IU/mL. The median historical lowest measured FVIII:C level was 0.22 IU/mL IQR [0.17–0.56] IU/mL for women with type 1 and 0.36 IU/mL IQR [0.14–0.64] for women with type 2. Table 2 shows the general baseline characteristics of the 19 women during their first reported pregnancy.

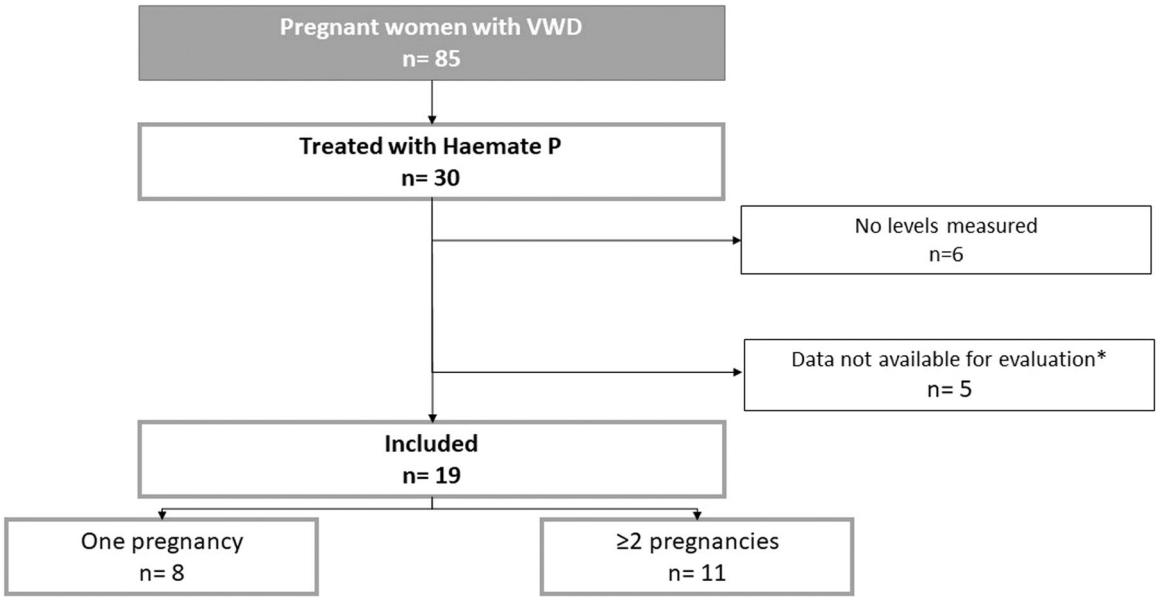

FIGURE 1 **Study population selection**. *No Informed consent or no participation in previous studies. VWD, Von Willebrand disease.

Observed VWF and FVIII levels compared to predefined target levels

Fourteen (74%) women were treated according to Dutch guidelines of 2009 (group A) and five (26%) women according to guidelines of 2020 (group B). Thirteen women (68%) had VWF:Act and FVIII:C peak levels measured after the first administration of VWF/FVIII concentrate during delivery. All target VWF:Act and FVIII:C peak levels were achieved (Figure 2). All measurements were taken within 2 h after administration, except for one measurement which was taken after 5.5 h. This last measurement was still above the predefined target level for VWF:Act and FVIII:C. Median VWF:Act peak level was 1.39 IU/mL IQR [1.08–1.5] for group A ($n = 7$) and 1.94 IU/mL IQR [1.53–2.35] for group B ($n = 5$). The median FVIII:C peak level was 1.95 IU/mL IQR [1.53–3.00] for group A and 2.91 IU/mL IQR [1.69–3.10] for group B. VWF:Act and FVIII:C trough levels were all ≥0.5 IU/mL (Figure 2) during the first 72 h of treatment in both groups. The median trough level of all VWF:Act measurements after the initial VWF/FVIII concentrate administration was 0.97 IU/mL IQR [0.80–1.11] for group A (24 observed levels out of 58) and 1.12 IU/mL IQR [0.99–1.61] for group B (14 observed levels out of 25). The median FVIII:C trough level after the initial VWF/FVIII concentrate administration was 1.85 IU/mL IQR [1.45–2.53] for group A (24 observed levels out of 58) and 2.43 IU/mL IQR [1.78–3.35] for group B (15 observed levels out of 25). During treatment, FVIII accumulation was observed to result in high levels. The median trough level of FVIII:C after the first VWF/FVIII concentrate administration was 2.67 IU/mL IQR [1.95–3.03] ($n = 15$). On Day 1 after treatment, the median FVIII:C trough level was 1.78 IQR [1.51–2.15] ($n = 17$). On Day 2 after treatment, the median FVIII:C trough level was 1.88 IQR [1.72–2.46] ($n = 10$). On Day 3 after treatment, the median FVIII:C trough level was 2.52 IQR [1.85–2.83] ($n = 6$). Additionally, in all women ($n = 11$) the pretreatment FVIII:C level, measured a few hours before the first VWF/FVIII concentrate infusion, was ≥1.0 IU/mL, except in one woman with type 2 N. This was significantly higher compared to third-trimester FVIII levels (median increase of 0.42 IQR [0.12–0.92]). Notably, one woman with VWD type 2 N who showed no increase and had a pretreatment FVIII level of 0.02 IU/mL was excluded from this increase.

Treatment and postpartum hemorrhage

All women received prophylactic treatment with VWF/FVIII concentrate to prevent PPH. The median treatment duration with VWF/FVIII concentrate was 3 days [IQR: 2–4]. In 18 of these women, additional treatment with tranexamic acid was given. In all cases, the initial dosage of tranexamic acid was 1000 mg, administered intravenously followed by oral administration with a dosage of either 1000 mg three times daily ($n = 4$) or 1000 mg four times daily ($n = 14$). Seventeen women had treatment prescribed for 7 days and one for 10 days. Because there was an option to extend the treatment if vaginal bleeding persisted, the actual long-term treatment duration with tranexamic acid is unknown. In one patient with type 2B VWD, no prophylactic platelet transfusion was required as her platelet counts were monitored and observed to be 43×10^9/L during delivery with no decrease during the postpartum period.

Sixteen (84%) women had a vaginal delivery and three women had a cesarean section (planned cesarean section $n = 1$; emergency cesarean $n = 2$). Regarding PPH, in total, nine (47%) women experienced PPH; six (32%) women experienced blood loss between 500 and 1000 mL, and three (16%) had an estimated blood loss ≥1000 mL. Among the latter group, one woman underwent a cesarean section and experienced a blood loss of 1500 mL, and two women had vaginal delivery with blood losses of 2500 and 1500 mL, respectively. Among these women with PPH, three women had a type 1 (3/6; 50%) and six women with type 2 VWD (6/13; 64%), which was not significantly different ($p = 1.0$). Moreover, among women treated according to the guidelines of 2009 (group A), eight women (8/14; 57%) experienced PPH; for 2020 (group B), one woman (1/5; 20%) experienced PPH, which was not significantly different ($p = 0.30$). Different obstetric risk factors were present (Supporting Information S1: Table 1). In 17 pregnancies (17/19; 90%), ≥1 obstetric risk factor was present. The most frequent obstetric risk factor was previous PPH (3/4; 75%, 15 women were primiparous) followed by

TABLE 2 General characteristics of the study population.

	n (%) or median [IQR]		
	Total	Type 1	Type 2[a]
No. of patients	19	6 (42)	13 (58)
Age, years	28 [24–30]	24 [22.5–26.75]	29 [26–32.50]
Body weight[b], kg (*n* = 17)	75 [71.75–85]	76.5 [73.5–82.5]	75 [70–99]
Disease			
Blood group O	9 (47)	4 (67)	5 (39)
Third trimester[c] VWF/FVIII levels (*n* = 18)			
VWF Antigen, IU/mL	0.68 [0.38–0.96]	0.66 [0.22–0.80]	0.69 [0.40–1.09]
VWF Activity, IU/mL	0.26 [0.15–0.45]	0.45 [0.14–0.63]	0.23 [0.14–0.38]
FVIII, IU/mL	1.09 [0.69–1.43]	0.99 [0.81–1.62]	1.18 [0.62–1.35]
Obstetrics			
Nullipara	15 (79)	5 (83)	10 (77)
Previous primary PPH	3	1	2
Vaginal delivery	16 (84)	5 (83)	11 (85)
Treatment			
Pretreatment VWF/FVIII levels[d] (*n* = 12)			
WF Antigen, IU/mL	1.41 [0.67–1.93]	1.08 [–]	1.48 [0.73–2.58]
VWF Activity, IU/mL	0.38 [0.21–0.74]	0.85 [–]	0.32 [0.17–0.64]
FVIII, IU/mL	1.52 [1.13–2.19]	1.83 [–]	1.20 [1.13–2.15]
Treatment duration, days	3 [2–4]	2.5 [1–4.5]	3 [3–4]
Haemate®P (FVIII) consumption[e] (*n* = 17)			
Initial dosage			
Target activity >1.0, FVIII IU/kg (*n* = 12)	32.6 [23.5–39.9]	31.3 [22.5–45.6]	33.9 [24.0–39.5]
Target activity >1.5, FVIII IU/kg (*n* = 5)	53.3 [38.9–69.8]	27.8 [–]	57.0 [50.8–74.4]
Primary PPH[f]			
Blood loss 500–1000 mL	6 (32)	1 (17)	5 (39)
Blood loss ≥1000 mL	3 (16)[g]	2 (33)	1 (8)
Secondary PPH[h]	5 (31)	2 (33)	3 (23)
Thrombosis	0	0	0

Abbreviations: FVIII, factor 8; IU/mL, international units per milliliter; median, [IQR = inter quartile range 25%–75%]; kg, kilogram; No., number (percentages); PPH, postpartum hemorrhage; VWF, von Willebrand factor.

[a]4 type 2 A, 1 type 2B, 5 type 2 M, and 1 type 2 N.

[b]Body weight was measured (or reported) in the third trimester except for one woman measured in the second trimester.

[c]Third trimester, ≥28 weeks of gestational age.

[d]Pretreatment levels were levels measured ≤24 h before delivery, and before initial dosage of Haemate®P.

[e]Haemate®P consumption, initial dosage (FVIII in IU) divided by body weight (kg), group 1 was treated according to old guideline with prescribed VWF:Act/FVIII:C peak level ≥1.0 IU/mL at delivery, group 2 was treated according to new guideline with prescribed VWF:Act/FVIII:C peak level ≥1.5 IU/mL at delivery.

[f]Postpartum hemorrhage, defined as blood loss ≥500 mL for vaginal delivery and ≥1000 mL for caesarean section; primary PPH, blood loss in first 24 h after delivery.

[g]Three women with blood loss ≥1000 mL, one woman with cesarean section, and two with vaginal delivery.

[h]Only reported and treated secondary PPH.

episiotomy or perineal lacerations (12/18; 67%) and retained placenta (3/19;16%).PPH frequency per obstetric factor is shown in Supporting Information S1: Table 1.

In five women (26%), secondary PPH which required additional treatment was reported. In two of these women, this was classified as secondary PPH related to retained placenta. Three women (60%) received treatment with additional administration of VWF/FVIII concentrate and tranexamic acid and two women (40%) with only tranexamic acid. One woman with VWD type 2 N and retained placenta was readmitted to the hospital for 6 days and required a red blood cell transfusion (two units) following tranexamic acid and additional VWF/FVIII concentrate. The same woman suffered from substantial blood loss later on, which required 2 days of treatment with VWF/FVIII treatment at home.

Comparison of pregnancies in women with more than one pregnancy

Eleven women (58%) had multiple pregnancies, each of which met the inclusion criteria. Of these 11, nine women (81%) had two pregnancies and two (19%) had three pregnancies. Four (36%) of these 11

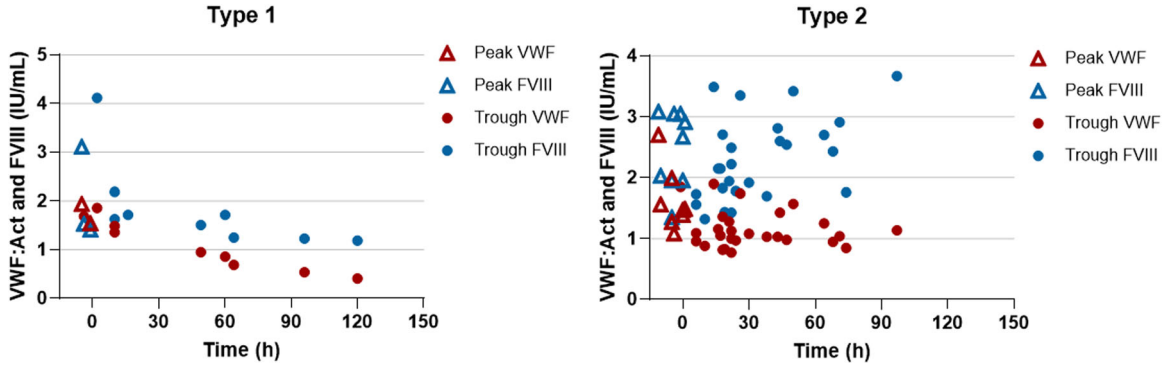

FIGURE 2 **Achieved VWF:Act/FVIII:C levels during treatment**. The graph on the right for patients with type 1 VWD and the graph on the left for patients with type 2 VWD. Peak VWF:Act/FVIII:C levels are shown <0 h. VWF:Act/FVIII:C trough levels are shown after $t = 0$. Time of childbirth was defined as $t = 0$ h. FVIII, factor VIII; h, hours; VWF:Act, von Willebrand activity.

women experienced recurrent PPH in each pregnancy and two (18%) women experienced PPH in only one pregnancy, with no recurrence in subsequent pregnancies. For all pregnancies, the chosen target factor level was based on the guideline applied at that time. Data on pretreatment factor levels were available for every pregnancy in only three of the 11 women. In these three women, the increase in pretreatment VWF:Act and FVIII:C levels was comparable for each pregnancy. The characteristics of these 11 women and their pregnancies are described in Table 2 in the Supporting Information Files.

Pharmacokinetics of VWF and FVIII

A total of 95 VWF:Act and 99 FVIII measurements were available to develop the PopPK model. None of the VWF:Act and FVIII levels were below the quantification limit of the essay (<0.02 and <0.01, respectively), and no levels were excluded from the analysis.

A one-compartment model described the VWF:Act and FVIII:C levels over time adequately. IIV could be estimated for the CL and V of VWF. The FVIII IIV could only be quantified for CL. The residual variability was best described by a proportional error model for VWF, and a combined additive and proportional error model for FVIII. The CL and V were not correlated with lean body mass, age, VWD type, blood group, VWF/FVIII levels in the third trimester, mode of delivery, and duration of delivery. Allometric body weight scaling on the PK parameters was used since lean body mass did not result in a better model fit. In Table 3, the parameter estimates of the final model are displayed. The bootstrap parameters were comparable with the estimated parameters of the final model.

Goodness-of-fit (GOF) plots display a good agreement between the predicted and observed VWF and FVIII levels (Supporting Information S1: Figures 1 and 2). The pcVPC for both VWF and FVIII activity levels showed that the observed data points were within the model-predicted range (Supporting Information S1: Figure 3).

The alignment of predicted and observed VWF:Act and FVIII levels, the pcVPC results, and the similarity between bootstrap and estimated parameters of the final model indicate the robustness and accuracy of the model predictions.

DISCUSSION

To our knowledge, this study is the first large retrospective study to assess the VWF:Act and FVIII:C levels after the administration of a specific VWF/FVIII concentrate to prevent PPH during delivery and the postpartum period in women with VWD. Additionally, we constructed a PopPK model to evaluate the PK of VWF and FVIII during treatment.

This study demonstrates that the predefined target VWF:Act and FVIII:C peak levels were achieved with the prescribed dosing regimens. This applies for both targeted VWF:Act and FVIII:C peak levels of ≥1.00 and ≥1.50 IU/mL. Regarding trough levels, all women achieved VWF:Act and FVIII:C trough levels of ≥0.50 IU/mL within the first 72 h of treatment. Notably, the median trough level of all VWF:Act measurements after the initial administration of VWF/FVIII concentrate were well above the prescribed target of ≥0.50 IU/mL, with 0.97 IU/mL IQR [0.80–1.11] for group A and 1.12 IU/mL IQR [0.99–1.61] for group B). This highlights the challenges in determining optimal trough levels. However, these recommended target peak and trough levels are not evidence-based and therefore under debate. VWF and FVIII levels in healthy women during pregnancy rise to much higher levels, with VWF:Act up to 3.00 IU/mL and FVIII up to 2.00 IU/mL.[18] Moreover, despite achieving target levels, PPH incidence remained high in our study population, with 33% experiencing blood loss of 500–1000 mL and 16% experiencing blood loss of ≥1000 mL. This high incidence among women with VWD who received prophylactic treatment with VWF/FVIII concentrate to prevent PPH aligns with the findings of other studies.[4,15,30] Notably, there is a study population overlap between our study and the study of Stoof et al. The ongoing prospective, observational PRIDE study aims to determine whether increasing the target VWF:Act and FVIII:C levels from 1.00 to 1.50 IU/mL reduces PPH incidence. Women in our study were treated according to both target levels outlined in guidelines from 2008 and 2020. However, our study population is small and cannot answer the question of whether higher target levels reduce PPH incidence. We have to wait for the results of the PRIDE study.

Importantly, in all women, the pretreatment FVIII:C level was above ≥1.00 IU/mL ($n = 11$), except in one woman with VWD type 2 N. Additionally, this was significantly higher compared to third-trimester FVIII:C levels (an increase of 0.42 [0.12–0.92]; median [25%, 75%]). During treatment, FVIII:C trough levels remained high. Despite these high levels, no thrombosis was reported in our study population. A systematic review reports that thrombosis resulting from factor concentrate treatment is rare (prevalence of 3.6 per 1000 patients), typically occurring when FVIII trough levels are ≥2.00 IU/mL over an extended period or when FVIII trough levels ≥1.50 IU/mL are present combined with other thrombotic risk factor.[31] This systematic review, however, included solely nonpregnant patients with hemophilia and VWD, who received different factor concentrates with varying

TABLE 3 Population pharmacokinetic parameters of VWF and FVIII.

Parameter	VWF final model values (RSE%) [Shrinkage %]	VWF bootstrap median value [95% CI]	FVIII final model values (RSE%) [Shrinkage %]	FVIII bootstrap median value [95% CI]
Baseline (IU/mL)	0.359 (16)	0.363 [0.268–0.484]	1.18 (16)	1.11 [0.66–1.46]
CL (mL/h/70 kg)	250 (9)	249 [215–295]	76.8 (27)	70.8 [42.9–110]
V (mL/70 kg)	6490 (8)	6514 [5533–7388]	3580 (6)	3863 [3431–4421]
Inter-individual variability (CV%)				
Baseline	87.3 (11) [1]	83.1 [56.6–108]	67.1 (26) [4]	70.5 [46.6–283.7]
CL	29.6 (22) [25]	28.1 [15.0–45.4]	74.1 (36) [38]	74.4 [20.4–335]
Vd	21.5 (32) [31]	20.5 [8.91–34.1]	-	-
Residual variability				
Proportional error (%)	14.2 (11)	13.9 [10.2–17.0]	16.0 (15)	15.5 [9.75–20.0]
Additional error (IU/mL)	-		0.11 (30)	0.12 [0.03–0.19]

Formula PK parameters:

$CL = \theta_{CL} \times (\frac{Body\ weight}{70})^{0.75}$;

$V = \theta_V \times (\frac{Body\ weight}{70})^{1}$.

Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation calculated as $\sqrt{e^{\omega^2} - 1} \times 100$, RSE, relative standard error; V, volume of distribution.

VWF/FVIII ratios. Our study population may be more at risk for thrombosis due to pregnancy and treatment with VWF/FVIII concentrates, however, these women with VWD will face a significantly higher risk of bleeding. Therefore, both high VWF and FVIII levels are required at delivery without FVIII becoming excessively high in the postpartum period. The PopPK model, presented in our study, may help to predict FVIII rise and its inter-individual variability, thereby identifying women at risk for excessive increases who may require VWF-containing concentrate with lower or no FVIII content such as recombinant VWF concentrate.

Pregnancy is known to result in physiological changes that may significantly affect PK.[32] However, a significant gap exists between our knowledge of physiological changes in pregnancy and the consequences of PK of drugs as well as the clinical outcomes.[33] We observed that the typical value for VWF CL was estimated to be 250 mL/h/70 kg, consistent with findings in non-pregnant individuals receiving Haemate®P to prevent bleeding during surgery as reported by Bukkems et al. (CL of 252 mL/h/70 kg for VWF).[28] However, there was a notable difference in the estimated Vd for VWF between our study and the findings of Bukkems et al. Our study estimated a Vd value of 6490 mL/70 kg, 28% higher than the value reported by Bukkems et al. (5060 mL/70 kg). This difference in Vd is probably typical for our specific study population, influenced by pregnancy-related changes in blood volume, cardiac output, and tissue perfusion, which can impact drug distribution. Moreover, in our study, we reported a CL and Vd for FVIII as 76.8 and 3580 mL/h/70 kg, respectively. Bukkems et al. reported a CL and V for FVIII of 517 mL/h/70 kg (when VWF:Act is 1.39 IU/mL) and 4440 mL/h/70 kg, respectively. Overall, our study population showed a 75% lower FVIII CL and a 19% lower FVIII Vd compared to non-pregnant women. These differences may be influenced by various factors, including physiological changes in pregnancy and increased endogenous pretreatment levels of VWF, which can impact FVIII CL. Consequently, the administration of VWF further reduces the CL of administered FVIII. Importantly, over time, different assays were used to measure VWF activity. The use of different assays may have inflated inter-individual variability in clearance and residual variability in the PopPK model. However, for VWF:Act, these values (29.6% and 14.2%, respectively) were low, indicating that the influence of these varying assays on the parameter estimates was negligible.

Although our study population is the largest population studied so far, the sample size remains limited to adequately study the differences between VWD types, the influence of obstetric risk factors, and covariates' influence on inter-individual variability of PK parameters. None of the studied covariates were significant, probably due to the relatively small sample size. Additionally, the small sample size and limited representation of different type 2 VWD patients (especially type 2 N and type 2B), as well as the lack of postpartum blood samples measuring factor levels over an extended period, may have affected the accuracy of the developed PopPK model. This is particularly true for patients with various subtypes of type 2 VWD and those with a longer duration of treatment. Furthermore, it is important to consider that our study included women with a more severe clinical phenotype of VWD, as patients with historically lowest VWF levels ≤0.30 and/or FVIII levels ≤0.40 were defined in the inclusion criteria. However, these patients have a higher risk of inadequate increases in their factor levels during pregnancy, making them more likely to require treatment with a VWF/FVIII concentrate during child delivery and the postpartum period.[10] Moreover, during selection for this study, five women had no informed consent and six women (6/30, 20%) had no data or significant missing data on the monitoring levels and could not be included. Unfortunately, blood sampling during replacement treatment in pregnant women is not standard of care, primarily due to logistics challenges. Therefore, we emphasize the importance of treatment monitoring in this population, especially since replacement treatment is not always sufficient to prevent PPH. In addition, due to a retrospective design with missing data, analyses were limited such as comparing pretreatment levels between pregnancies within the same woman. Finally, visual estimation of blood loss is prone to inter-observer bias and may also have influenced PPH incidence, especially in borderline cases. However, it should be realized that reports show that visual estimated blood loss is generally an underestimation of total blood loss.[34]

In summary, in our study, the predefined targeted VWF:Act and FVIII:C peak levels according to the applied guideline were achieved with prescribed dosing regimens. However, a high PPH incidence was

observed despite this achievement. Furthermore, PK of specific VWF/FVIII concentrate, especially FVIII CL postpartum, was lower in pregnant women compared to non-pregnant individuals. Importantly, future prevention of PPH involves the consideration of multiple factors including obstetric risk factors, as well as optimal treatment of VWD, along with identifying the best VWF and FVIII target levels. The latter can be achieved by gaining a better understanding of the course of both endogenous and treatment-provided exogenous VWF and FVIII levels through the standardization of blood sampling and using supportive PopPK modeling specifically for women to predict VWF and FVIII levels during pregnancy and the postpartum period.

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AUTHOR CONTRIBUTIONS

Wala Al Arashi designed the study. Wala Al Arashi and Michael E. Cloesmeijer interpreted and analyzed data. Wala Al Arashi wrote the manuscript. Michael E. Cloesmeijer, Frank W. G. Leebeek, Marieke J. H. A. Kruip, Johannes J. Duvekot, Ron A. A. Mathôt, and Marjon H. Cnossen critically revised the manuscript. Marjon H. Cnossen supervised the study. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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